Original Article

Association between health-related quality of life and perioperative exercise capacity in older postoperative patients with non-small cell lung cancer

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Background: Lung cancer represents a significant global health concern and constitutes the primary cause of cancer-related mortality. Complete surgical resection with curative intent remains the most efficacious treatment modality for improving the survival rate of patients with localized lung cancer. Average life expectancy has increased in many countries, and the number of older patients undergoing surgery has increased. We aimed to evaluate the change in health-related quality of life (HRQOL) during perioperative lung resection and the association between HRQOL and perioperative physical function (PF) in older patients with lung cancer.

Methods: This prospective observational study was conducted in a single tertiary university hospital. Patients aged ≥70 years who underwent lung resection between 1 April 2013 and 31 December 2020 were included. HRQOL was assessed utilizing the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) preoperatively and at 1, 3, and 6 months postoperatively. PF was evaluated using the handgrip, quadriceps force, and 6-minute walking distance (6MWD) tests preoperatively and 1 week after surgery. We analyzed a model for total HRQOL and each domain of HRQOL scores at different time points using a mixed-effects model for repeated measures. A multiple regression analysis was performed to estimate the associations between changes in total HRQOL scores following surgery and clinically relevant factors.

Results: In total, 260 patients (172 with stage IA disease, 162 men; median age, 75 years) were included in the analysis. The median preoperative total HRQOL score was 90.1 points, while the scores at postoperative 1, 3, and 6 months were 81.5, 87.5, and 87.4 points, respectively. The total HRQOL score at baseline and the decline in postoperative 6MWD were significant predictors of the total HRQOL score at each time point.

Conclusions: HRQOL recovered to preoperative levels 3 months after surgery; the 6MWD decrease before and after surgery was associated with HRQOL recovery than other clinically relevant factors. These results suggest the importance of active early mobilization in preventing functional decline during hospitalization and continuing exercise training after discharge.

Keywords: Exercise capacity; general surgery; non-small cell lung carcinoma; quality of life (QoL); rehabilitation

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Introduction

Background

Lung cancer represents a significant global health concern and constitutes the primary cause of cancer-related mortality (1). Complete surgical resection with curative intent remains the most efficacious treatment modality for enhancing the survival rate of patients with localized lung cancer (2). Average life expectancy has increased in many countries. Consequently, the number of older patients undergoing surgery has increased. Overall, 59% of patients who undergo surgery for primary lung cancer in Japan are over 70 years of age (3).

Rationale and knowledge gap

Health-related quality of life (HRQOL) is an important prognostic indicator in older patients who have undergone surgery for lung cancer. A review of the impact of lung resection on HRQOL in patients with lung cancer showed a consistent decline in the first 3 months (4-6). Schulte *et al.* reported that the decline in HRQOL after surgery in older patients with lung cancer was not fully reversed and that they were less likely than younger patients to achieve preoperative HRQOL levels (7). However, several studies have reported contradictory results (8-10), and there is no consensus regarding decreased postoperative HRQOL in older patients with lung cancer. Additionally, the clinically problematic characteristics of patients likely to have poor postoperative HRQOL have not yet been reported.

The predictive factors for postoperative HRQOL include preoperative pulmonary function (11), coexistence of chronic obstructive pulmonary disease (12), and surgical procedures (13). However, physical function (PF), which is likely related to postoperative HRQOL, has not been investigated.

Objective

We hypothesized that the postoperative decline in exercise capacity may be related to the postoperative HRQOL. We, therefore, aimed to identify changes in HRQOL before and after lung resection and the association between postoperative HRQOL and perioperative exercise capacity in older patients with lung cancer. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1265/rc).

Highlight box

Key findings

- Health-related quality of life (HRQOL) was assessed in older patients who underwent lung cancer surgery. It recovered to preoperative levels at postoperative 3 months. Reduced 6-minute walking distance (6MWD) before and after surgery was strongly associated with HRQOL recovery.

What is known and what is new?

- Research has shown that factors influencing postoperative HRQOL in patients with lung cancer include preoperative pulmonary function, concurrent chronic obstructive pulmonary disease, and the type of surgical procedures.
- This study demonstrated that the 6MWD decrease before and after surgery was associated with HRQOL recovery in older patients with lung cancer.

What is the implication, and what should change now?

- Evaluating exercise capacity before and after surgery is essential for older lung cancer patients. This assessment helps identify individuals who may experience delayed recovery of HRQOL in the post-surgical phase at an early point.

Methods

Study population

This study employed a prospective, observational design in which consecutive patients with preoperative clinical stage I to IIIA non-small cell lung cancer, who underwent lung resection between 1 April 2013 and 31 December 2020 at Nagasaki University Hospital, were enrolled. Patients aged ≥70 years and planning to undergo surgery for lung cancer were included. Patients with cognitive impairment that affected their answers to the questionnaire, those with recurrent or metastatic lung cancer in the 6-month follow-up period, those with surgical procedures performed for staging or histological diagnosis, and those who had undergone pneumonectomy or had a history of thoracic surgery were excluded from the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Human Ethics Review Committee of the Nagasaki University Hospital (approval No. 12092420-2) and informed consent

was taken from all individual participants.

Baseline characteristics

The following data were collected for the study participants: clinical stage of the cancer, pre-existing comorbidities, pulmonary function [forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, vital capacity (VC), and diffusing capacity of the lung for carbon monoxide (DLCO)], and nutritional status measured within 1 month prior to surgery. Pre-existing comorbidities were assessed using the functional comorbidity index (FCI) by reviewing medical records. This validated measure is based on 18 comorbidity items, with higher scores indicating more comorbidities (14). Pulmonary function tests were conducted utilizing a spirometer (CHSTAC-8900; Chest Corporation, Tokyo, Japan) in accordance with international guidelines (15). The predicted FVC and FEV_1 were calculated employing equations developed for healthy, nonsmoking Japanese individuals (16). Preoperative nutritional status was assessed using the Geriatric Nutritional Risk Index (GNRI), an established nutritional evaluation tool and predictor of morbidity and mortality in older adults (17).

Measurements

HRQOL assessment

HRQOL was assessed using the Japanese version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Questionnaires were administered 1 day before surgery and at postoperative months (POMs) 1, 3, and 6 for self-completion. The EORTC QLQ-C30 is an internationally validated cancer-specific HRQOL questionnaire (18). The questionnaire comprises 30 items, consisting of five multi-item functional scales [PF, role function (RF), cognitive function (CF), emotional function (EF), and social (SF)], three multi-item symptom scales [fatigue (FA), nausea and vomiting (NV), and pain (PA)], six single-item symptom scales [dyspnea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI), and financial impact (FI)], and a two-item global quality of life scale (QL). The questionnaire utilizes a four-point response format, with the exception of the QL scale, which is scored on a scale of 1 to 7. The scores range from 0 to 100; a high score on the functional scale indicates a high level of functioning, whereas a high score on the symptom scale indicates a high level of symptoms. Additionally, the QLQ-C30 summary score (QoL SumSc) was calculated to complement the 15-outcome profile generated using the QLQ-C30 (19). In this study, we operationally defined QoL SumSc as the total HRQOL score.

PF

The following tests were performed 1 to 2 days before surgery and on postoperative days 5 to 7. Four physiotherapists collected the data. The 6-minute walking test (6MWT) was utilized to evaluate functional exercise capacity, with the primary outcome measure being the 6-minute walking distance (6MWD). The test was performed according to published guidelines (20), and the better of the two attempts was recorded. A 30-m corridor was used for the test, with patients instructed to walk as far as possible within 6 minutes. Standardized verbal encouragement was administered at one-minute intervals. Oxygen saturation and pulse rate were continuously monitored throughout the test using a PULSOX-300 device (KONICA MINOLTA, Tokyo, Japan). The modified Borg scale was used to quantify the levels of DY and leg FA immediately after the test (21). The preoperative 6MWD minus the postoperative 6MWD was used as a measure of the decrease in the 6MWD.

Handgrip force (HF) and quadriceps force (QF) were measured as indices of skeletal muscle strength. HF was assessed using a dynamometer (T.K.K.5401; Takei-Kiki-Kogyou Corporation, Niigata, Japan) with the elbow flexed at 90°, and three attempts were conducted. The maximum value was recorded for both hands (kg). QF was evaluated as the peak force generated by the dominant leg during a maximal isometric knee extension maneuver in the seated position by using a hand-held dynamometer with a fixing belt (μ-Tas F-1; Anima Corporation, Tokyo, Japan) in accordance with a standard protocol (22). The highest value of at least three maneuvers was recorded and expressed in kilograms of force.

Surgical and perioperative management

Patients' selection for thoracoscopic surgery or thoracotomy based on the results of chest radiographic studies, bronchoscopy, general patient condition (performance status), and comorbidities (e.g., presence of interstitial lung disease). Postoperatively, epidural or continuous intravenous analgesia was used to manage postoperative incisional PA until the removal of the chest drain, after which oral

analgesics were administered.

Thoracotomy was defined as an incision of ≥6 cm and/or the use of a rib retractor. Complications that occurred during the postoperative hospital stay were defined. Postoperative complications (POCs) were diagnosed by a surgeon and/or radiologist and were identified from participant medical records according to the Clavien-Dindo classification (23), which categorizes POCs into five major groups based on the intervention required for patient care: grade 1, no pharmacological intervention other than antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy; grade 2, pharmacological intervention with medications other than those allowed for grade 1 complications; grade 3, further intervention without (3A) or with (3B) general anesthesia; grade 4, life-threatening complications and those requiring intensive care unit management; and grade 5, patient death. Patients with a severity greater than grade II were classified as having postoperative pulmonary complications (24). Postoperative management encompassed physiotherapy, which included early ambulation, airway clearance techniques, and general exercise training during hospitalization. Patients were given individualized post-discharge lifestyle guidance, encouragement to increase physical activity, and self-exercises before discharge. No physiotherapy was provided to the patients after discharge.

Statistical analysis

The Shapiro-Wilk test was used to examine the data distribution. Variables are expressed as median values and interquartile range (IQR) or as mean ± standard deviation values, number of patients, and percentage. A mixed-effects model for repeated measures (MMRM) was utilized to analyze the differences between HRQOL scores at 1, 3, and 6 months postoperatively compared to baseline HRQOL scores. In this model, time point was treated as the fixed effect, while patients were considered the random effect. In addition, multiple regression analyses were used to estimate the associations between changes in QoL SumSc after surgery and clinically relevant factors. The model included age and sex, QoL SumSc at baseline, FCI, preoperative DLCO, GNRI, surgical procedure, POCs, and decrease of 6MWD as independent variables. The results are presented as adjusted estimates with 95% confidence intervals. Because this was an exploratory study, no adjustment for multiplicity was planned. The level of significance was set at $P<0.05$ for all statistical tests. All analyses were performed using JMP software (version 15.0; SAS Institute Japan, Tokyo, Japan).

Results

Table 1 shows the characteristics of the 260 patients included in this study. Forty-eight patients developed POCs: prolonged air leakage for 4 days, 18 cases; pneumonia, 9 cases; atrial fibrillation, 8 cases; chylothorax, 6 cases; pleuritis, pyothorax, and acute exacerbation of interstitial pneumonia, 3 cases; and atelectasis, cerebrovascular accident, and pleural effusion, 1 case.

The median 6MWT distance decreased from 490 m at baseline to 443 m after surgery. Oxygen desaturation during the 6MWT was 2% preoperatively and 4% postoperatively. DY severity, measured by the modified Borg scale, was 4 at the conclusion of the preoperative 6MWT and 5 postoperatively.

Perioperative changes in EORTC QLQ-C30 score and QLQ SumSc

The median preoperative total QoL SumSc, representing the total HRQOL score, was 90.1 points; the scores at postoperative 1, 3, and 6 months were 81.5, 87.5, and 87.4 points, respectively (*Figure 1*). Detailed information regarding the individual HRQOL scores at each time point is presented in Table S1. *Table 2* presents the outcomes of the MMRM analysis of individual HRQOL scores based on preoperative values. The table delineates the preoperative value as 0 and presents the individual HRQOL scores at each time point relative to this baseline. In QoL SumSc, used as the total HRQOL score, the fixed effect by time point was significant. The estimated differences in QoL SumSc from baseline were −5.37 (95% CI: −6.65 to −4.08) at POM1, 1.15 (95% CI: −0.43 to 2.74) at POM3, and 1.79 (95% CI: −0.08 to 3.66) at POM6. Additionally, most functional scales (PF, RF, EF, and SF) and symptom scales (FA, PA, DY, SL, and AP) exhibited a similar pattern, except for DY, which failed to recover during the POM3 period.

Postoperative EORTC QLQ-C30 SumSc and pre- and postoperative factors

A multiple regression analysis was performed to assess the impact of age and sex, QoL SumSc at baseline, FCI, preoperative DLCO, GNRI, surgical procedure, POCs, and decrease in 6MWD on postoperative HRQOL. As a result,

Table 1 Baseline patient characteristics (n=260)

Variable	Median [IQR] or n [%]
Age, years	75 [72–79]
Sex, male	162 [62]
Body mass index, kg/m^2	22.8 [20.3–24.8]
Comorbidity	
Pulmonary	112 [43]
Cardiac	67 [26]
Hypertension	140 [54]
Diabetes	53 [20]
Other	41 [16]
Smoking status	
Never	148 [57]
Ever and current	112 [43]
Pack/years	13 [0–50]
Preoperative lung cancer stage	
Stage IA/IB	172 [66]/39 [15]
Stage IIA/IIB	17 [7]/15 [6]
≥ Stage IIIA	17 [7]
Prior adjunct treatment	
No treatment	255 [98]
Chemotherapy and/or radiotherapy	5 [2]
ECOG-PS	
0	225 [87]
1	33 [13]
≥2	2 [1]
Preoperative physical function	
6MWD, m	490 [439–537]
HF, kg	27.1 [20.5–33.7]
QF, kg	28.9 [21.5–37.5]
Preoperative nutritional status	
GNRI	106 [100–112]
Preoperative pulmonary function	
FEV_1, L	2.06 [1.80–2.44]
FEV_1, % pred.	105 [91–119]
FVC, L	2.99 [2.44–3.59]
FVC, % pred.	107 [98–118]
FEV_1/FVC, %	74 [66–80]
VC, L	3.05 [2.47–3.63]
VC, % pred.	109 [99–120]
DLCO, mL/min/mmHg	14.1 [11.4–16.9]
DLCO, % pred.	99 [80–116]
Surgical procedure	
Thoracoscopy	150 [58]
Thoracotomy	110 [42]
Resection	
Wedge	17 [7]
Segmentectomy	27 [10]
Lobectomy	216 [83]
Duration of surgery, min	208 [168–255]
Blood loss, g	66 [23–150]
Length of stay, day	13 [10–16]

6MWD, 6-minute walk distance; DLCO, diffusing capacity of the lung carbon monoxide; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GNRI, Geriatric Nutritional Risk Index; HF, handgrip force; IQR, interquartile range; QF, quadriceps force; VC, vital capacity.

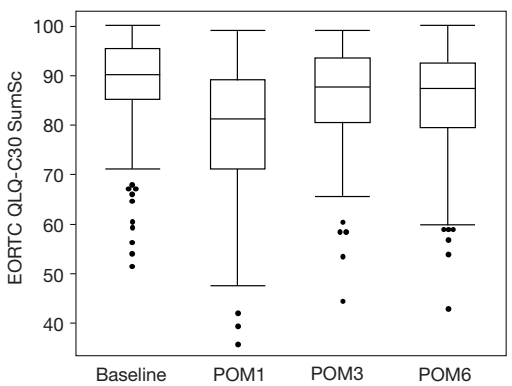

Figure 1 Box plot of QoL SumSc. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; POM, postoperative month; QoL SumSc, quality of life summary score.

Table 2 Perioperative changes of EORTC QLQ-C30 and summary scores in patients who received both the preoperative and postoperative QoL questionnaires

Instrument	POM1 (n=171)		POM3 (n=78)		POM6 (n=76)	
	Mean estimate (95% CI)	P	Mean estimate (95% CI)	P	Mean estimate (95% CI)	P
PF	−5.93 (−7.65 to −4.21)	<0.001	0.72 (−1.40 to 2.84)	0.50	1.05 (−1.45 to 3.56)	0.41
RF	−9.92 (−12.49 to −7.33)	<0.001	2.12 (−1.05 to 5.28)	0.19	2.534 (−1.22 to 6.29)	0.19
CF	0.36 (−1.58 to 2.29)	0.72	0.92 (−1.49 to 3.33)	0.45	−2.44 (−5.29 to 0.40)	0.09
EF	−2.02 (−3.84 to −0.20)	0.03	3.11 (0.60 to 5.62)	0.02	1.79 (−0.95 to 4.52)	0.20
SF	−5.74 (−7.82 to −3.67)	<0.001	2.19 (−0.38 to 4.76)	0.09	2.61 (−0.44 to 5.66)	0.09
FA	7.99 (5.78 to 10.19)	<0.001	0.58 (−2.17 to 3.34)	0.68	1.13 (−2.11 to 4.38)	0.49
NV	0.23 (−1.15 to 1.62)	0.74	−1.78 (−3.46 to −0.09)	0.03	−1.06 (−3.06 to 0.96)	0.30
PA	12.99 (10.48 to 15.50)	<0.001	−4.65 (−7.71 to −1.59)	0.003	−7.74 (−11.38 to −4.10)	<0.001
DY	9.27 (6.57 to 11.98)	<0.001	5.25 (1.93 to 8.58)	0.002	−0.26 (−4.21 to 3.68)	0.90
SL	4.78 (1.89 to 7.66)	0.001	−3.22 (−6.77 to 0.33)	0.08	−5.25 (−9.45 to −1.07)	0.01
AP	8.46 (5.96 to 10.97)	<0.001	0.42 (−2.65 to 3.49)	0.79	−4.18 (−7.82 to −0.53)	0.02
CO	−0.74 (−3.63 to 2.14)	0.61	−0.86 (−5.64 to 3.92)	0.72	2.21 (−2.60 to 7.02)	0.37
DI	−0.19 (−1.19 to 0.81)	0.71	−0.85 (−4.40 to 2.70)	0.64	−1.60 (−5.80 to 2.60)	0.46
FI	0.30 (−1.55 to 2.15)	0.75	−1.22 (−3.49 to −1.06)	0.29	−0.42 (−3.13 to 2.30)	0.76
QL	−6.91 (−9.50 to −4.32)	<0.001	3.86 (0.64 to 7.08)	0.02	3.12 (−0.69 to 6.93)	0.11
SumSc	−5.37 (−6.65 to −4.08)	<0.001	1.15 (−0.43 to 2.74)	0.15	1.79 (−0.08 to 3.66)	0.06

Results of analysis of variance for repeated measurements based on preoperative values. CI, confidence interval; AP, appetite loss; CF, cognitive function; CO, constipation; DI, diarrhea; DY, dyspnea; EF, emotional function; FA, fatigue; FI, financial impact; NV, nausea and vomiting; PA, pain; PF, physical function; QL, global quality of life scale; QoL, quality of life; POM, postoperative month; RF, role function; SF, social; SL, insomnia; SumSc, summary score; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

a decrease in postoperative 6MWD at all time points was a significant predictor of postoperative total HRQOL score (coefficients 0.067, 95% CI: 0.027–0.106, P=0.001 at POM1; coefficients 0.096, 95% CI: 0.042–0.149, P=0.001 at POM3; coefficients 0.051, 95% CI: 0.002–0.101, P=0.04 at POM6). In contrast, age, sex, comorbidity, preoperative nutritional status, pulmonary function, surgical procedure, and POCs were not significantly associated with the outcomes. A summary of these findings is presented in *Table 3*.

Discussion

Key findings

Some postoperative QoL scores decreased 1 month after surgery and recovered by POM3. Furthermore, the decrease in 6MWD after surgery was an independent predictor of the decrease in postoperative HRQOL.

Strengths and limitations

To the best of our knowledge, this study represents the first investigation into the impairment of HRQOL in the early postoperative period following lung resection for lung cancer in older patients and the examination of predictor variables. Nevertheless, the present study is subject to several limitations. First, there is a paucity of patient data. Notably, POM6 exhibits a high attrition rate for HRQOL assessment, suggesting that the results at this stage may be considered merely indicative. Second, it was conducted at a single center with a relatively small sample size. To address this limitation, larger multicenter studies are needed to further examine the characteristics of postoperative HRQOL in older patients with lung cancer. Third, the

Table 3 Results of multiple linear regression analysis

Variable	Coefficients	95% CI	P value
1 month postoperatively			
Baseline QoL SumSc, point	0.629	0.386–0.872	<0.001
Postoperative 6MWD decline, m	0.067	0.027–0.106	0.001
3 months postoperatively			
Baseline QoL SumSc, point	0.369	0.010–0.728	0.04
Postoperative 6MWD decline, m	0.096	0.042–0.149	0.001
6 months postoperatively			
Baseline QoL SumSc, point	0.959	0.546–1.372	<0.001
Postoperative 6MWD decline, m	0.051	0.002–0.101	0.04

Results are based on a multiple regression model including age, sex, comorbidity, preoperative nutritional status, pulmonary function, surgical procedure, and postoperative complications as independent variables. 6MWD, 6-minute walk distance; CI, confidence interval; QoL SumSc, quality of life summary score.

study was limited to three evaluation time points: POMs 1, 3, and 6. To provide a more detailed understanding, it would be beneficial to conduct evaluations at multiple time points, as in a study by Nugent *et al.* (25). Finally, we were unable to assess the participants' physical activity levels after discharge. Consequently, the reason for the delayed recovery of HRQOL in patients with a greater decline in exercise capacity remains unclear.

Comparison with similar research

The HRQOL in older patients with lung cancer recovered to its preoperative state 3 months after surgery, as shown by a previous study that used the QoL SumSc measure, which showed a decrease in QoL SumSc at the POM3 mark (26). When comparing the results of the previous study with those of our study, the PF, RF, and SF domains showed less recovery in the previous study. This may be attributed to the inclusion of patients who underwent pneumonectomy in the previous study. A previous study on pneumonectomy reported a more negative impact on the physical QoL compared with lobectomy (24). Nugent *et al.* (25) demonstrated that HRQOL was reduced after surgical treatment for lung cancer and tended to recover after 2 months. Our results aligned with this pattern, suggesting that postoperative HRQOL may recover in 2–3 months among older patients with lung cancer. However, recovery from DY tends to be prolonged, which was also the case in a previous review (26). Therefore, measures are required to improve postoperative DY in older patients with lung cancer.

Explanations of the findings

The decrease in the 6MWD after surgery was more strongly associated with HRQOL recovery than other clinically relevant factors. According to Pompili *et al.* (27), preoperative PF, as measured by the PF domain of the QoL score, was associated with postoperative physical QoL. However, the impact of pre- and postoperative changes in PF on postoperative HRQOL has not yet been studied. Zhou *et al.* (28) reported that physical activity is low among patients who have undergone surgery for lung cancer and may not recover within 3 months following surgery. This decline in physical activity may be more significant in patients with a greater decline in motor function during hospitalization, which could delay the recovery of HRQOL. However, physical activity was not assessed in this study. Although several previous studies have shown that age, sex, and lung function are predictors of postoperative HRQOL (11,27,29), these factors were not significant contributors in this study. This phenomenon may be attributed to the restricted age range of the study population, which included only patients aged 70 years and older. Moreover, the age criterion for respiratory function was set at 70 years and above, potentially leading to more stringent parameters for surgical indications and a reduced number of patients with compromised respiratory function.

Conclusions

The current investigation revealed that the HRQOL of older patients with lung cancer tends to recover within 3 months following surgery. However, this recovery may be protracted in individuals who experience a substantial postoperative decrease in exercise capacity. Measuring the exercise capacity of older patients undergoing lung resection for lung cancer could help identify those at risk of delayed recovery of postoperative HRQOL. Furthermore, these findings emphasize the need for early active mobilization during hospitalization and the continuation of exercise training after discharge to improve exercise capacity and enhance the recovery of postoperative HRQOL.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Human Ethics Review Committee of the Nagasaki University Hospital (approval No. 12092420-2) and informed consent was taken from all individual participants.

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